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VIA FEDERAL EXPRESS

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CITIZEN PETITION
-EXPEDITED DECISION REQUESTED-

The undersigned, on behalf of Apotex, Inc., the TorPharm Division of Apotex, Inc. and Apotex Corporation (collectively, "Apotex") submit this petition under 21 C.F.R. §§ 10.25(a), 10.30 and 314.53, to request the Commissioner of Food and Drugs ("the Commissioner") to expedite review of this petition and to issue prior to February 29, 2000, the following ruling and administrative action, together with appropriate implementation orders, pursuant to 21 U.S.C. §§355(b) and (j) of the Federal Food, Drug and Cosmetic Act ("the Act"):

> SmithKline Beecham Corporation has violated the statutory requirements of 21 U.S.C. §§ 355(b)(1) and (c)(2) and FDA's regulations by submitting patent information on U.S. Patent Nos. 5,900,423 and 5,872,132 on anhydrate forms of paroxetine hydrochloride for publication in Approved Drug Products with Therapeutic Equivalence Evaluations ("the Orange Book") in connection with previously approved New Drug Application No. 020-031 for paroxetine hydrochloride hemihydrate. U.S. Patent Nos. 5,900,423 and 5,872,132 shall be removed from the Orange Book immediately.

00P-0499

CP1

SmithKline Beecham Corporation ("SmithKline") has systematically and unlawfully used the statutory and FDA patent listing procedures to stifle generic competition. Apotex and the public are suffering real and direct harm as a result. The Act entrusts FDA to ensure appropriate patent listings in the Orange Book. Apotex thus petitions FDA to remove SmithKline's unlawfully listed patents from the Orange Book.

SmithKline is the holder of New Drug Application ("NDA") No. 020-031 on crystalline paroxetine hydrochloride hemihydrate, which FDA approved on December 29, 1992, with listed U.S. Patent No. 4,721,723, Anti-Depressant Crystalline Paroxetine Hydrochloride Hemihydrate ("the '723 hemihydrate patent") (Tab A).

On March 31, 1998, Apotex filed Abbreviated New Drug Application ("ANDA") No. 075-356 on an anhydrous paroxetine hydrochloride drug product. Pursuant to 21 U.S.C. §§ 355(j)(2)(A)(vii)(IV) and (j)(5)(B)(iii), Apotex filed a certification of noninfringement ("paragraph IV certification") of the '723 hemihydrate patent and served the required notice on SmithKline.

On June 26, 1998, SmithKline filed a statutory patent infringement action against Apotex under 21 U.S.C. §355(j)(5)(B)(iii) and 35 U.S.C. §271(e)(2) in the U.S. District Court for the Northern District of Illinois. This case has advanced substantially toward judgment.

In May, 1995, more than two years after FDA approved NDA 020-031, SmithKline began filing patent applications with the U.S. Patent and Trademark Office ("the PTO") for purportedly new anhydrous polymorphs of paroxetine hydrochloride. In 1999, the PTO issued U.S. Patent No. 5,872,132 ("the '132 Form C patent") (Tab B) and U.S. Patent No. 5,900,423 ("the '423

Form A patent") (Tab C) for purportedly new anhydrous forms of paroxetine. SmithKline violated the Act by causing FDA to list the 1999 patents in connection with NDA 020-031.

Apotex followed the Act and submitted paragraph IV certifications of noninfringement (and, in the case of the '423 Form A patent, invalidity and unenforceability) for SmithKline's improperly listed patents. (Tabs D, E). On August 9, 1999, SmithKline filed a new statutory patent infringement action against Apotex on the '423 Form A patent in the U.S. District Court for the Eastern District of Pennsylvania.

Apotex appropriately sought to avoid incongruent stays of approval by moving to transfer and consolidate the pending suits. However, SmithKline opposed the motion and succeeded. The District Court in Philadelphia denied the motion to transfer on January 4, 2000.

Apotex now must defend a second Hatch-Waxman suit on its one ANDA 075-356. Apotex seeks expedited relief in this petition, because each passing day continues to drain resources toward a second expensive lawsuit that Apotex should not be facing. There also is a real and substantial threat that Apotex, which presented the first ANDA with a paragraph IV certification on the '723 hemihydrate patent, will lose the benefit of the 180-day period of market exclusivity provided by 21 U.S.C. §355(j)(5)(B)(iv) due to staggered court rulings.[1]

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[1] No other generic company has received approval of an ANDA on paroxetine hydrochloride. To Apotex's knowledge, the only other company that has filed an ANDA is Geneva Pharmaceuticals, and its ANDA is far behind Apotex's application in the queue in the Office of Generic Drugs. Accordingly, there is no possibility that Apotex could mitigate its loss by bargaining for a selective waiver of its period of market exclusivity as suggested in *Granutec, Inc. v. Shalala*, 139 F.3d 889, 1998 WL 153410, at **5-6 (4th Cir. Apr. 3, 1998) (Tab F).

Making matters worse, SmithKline apparently has more patents in the pipeline. Each new patent, upon listing, may lead to new litigation which may indefinitely stall market opportunities for generic drugs. Specifically, on December 28, 1999, the PTO issued and published U.S. Patent No. 6,007,842, Paroxetine Tablets and Process to Make Them ("the '842 tablet patent") (Tab M). SmithKline, for unknown reasons, postponed the patent's issuance. However, SmithKline also filed a continuation of the patent application, and the patent may issue in the same or altered form in the future.

Apotex requests expedited consideration of this citizen petition pursuant to 21 C.F.R. §§ 10.25(a), 10.30 and 314.53(f) because SmithKline's continuing pattern of abuse of the patent listing requirements of 21 U.S.C. §355(c)(2) threatens the operation of the Hatch-Waxman ANDA procedure, which Congress designed to expedite the introduction of low-cost generic competition.

A. Action Requested

This petition requests that:

1. The Commissioner rule, no later than February 29, 2000, that the '132 Form C patent and the '423 Form A patent are not properly listed in the Orange Book, because SmithKline failed to meet the statutory requirements of 21 U.S.C. §355(c)(2) in supplying patent information on these patents for listing in the Orange Book in connection with NDA 020-031;

2. The Commissioner issue an order, no later than Februrary 29, 2000, that effectively removes the '132 Form C patent and the '423 Form A patent from the Orange Book; and

3. The Commissioner refuse to permit any activity with respect to the '423 patent, the '132 patent and any future issued SmithKline patents to interfere with or delay FDA's review and approval of Apotex's ANDA No. 075-356.

B. Statement of Grounds

Introduction.

The critical issue is whether FDA will endorse SmithKline's program to thwart the introduction of generic competition for its Paxil® drug product by the serial publication of new patents in the Orange Book years after FDA approved SmithKline's NDA. SmithKline has manipulated FDA into listing patents in the Orange Book that fail to meet the listing requirements in three ways. **First**, SmithKline wrongly used the "late listing" provisions of §355(c)(2) to list patents that issued after NDA approval in the Orange Book. Section 355(c)(2) allows a "late listing" of a patent only if patent information was not previously submitted under 21 U.S.C. §355(b)(1). Since SmithKline submitted patent information for the '723 hemihydrate patent under 21 U.S.C. §355(b)(1), prior to NDA approval, SmithKline was precluded from listing additional patents subsequent to its 1992 NDA approval date. **Second**, SmithKline wrongly submitted patent information on patents which do not claim the FDA-approved drug that was the subject of its NDA 020-031. **Third**, SmithKline submitted patent information on patents that describe drugs for which SmithKline has submitted no safety or efficacy data in a new or supplemental NDA.

The net effect of SmithKline's actions is to delay, perhaps indefinitely, the introduction of generic competition through "blocking patents" that claim drugs that SmithKline is not marketing and has no intention of ever marketing, and which serve only to serially stay FDA approval of any ANDAs in connection with NDA 020-031. FDA should "de-list" SmithKline's '132 Form C and '423 Form A patents, because the patents fail to meet the statutory listing

requirements. FDA further should ensure that SmithKline does not list additional patents for NDA 020-031 in the future.

Argument.

1. SmithKline Cannot Take Advantage Of The Post-Approval Patent Listing Provisions Of 21 U.S.C. §355(c)(2), Because SmithKline Filed Patent Information On Its Paroxetine Hydrochloride Drug With Its NDA And Prior To FDA Approval.

(a) SmithKline's '132 Form C And '423 Form A Patents Were Applied For And Issued Too Late For Listing.

The Act requires patent information to be submitted with an NDA. 21 U.S.C. §355(b)(1). However, Congress recognized that proceedings in the PTO on a patent application might not be complete at the time when the applicant filed its NDA. Congress provided for this eventuality in an additional sentence in §355(b)(1):

> If an application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing date but ***before approval*** of the application, the applicant shall amend the application to include the information required by the preceding sentence.

Id. (emphasis supplied). SmithKline's '723 patent on crystalline paroxetine hydrochloride hemihydrate issued in 1988, and, on information and belief, SmithKline submitted the requisite patent information on the '723 hemihydrate patent either with its NDA on paroxetine hydrochloride hemihydrate or during the post-filing grace period before approval of the NDA.

Section 355(b)(1) does not provide for filing patent information subsequent to FDA's approval of an NDA. However, Congress recognized that, in some instances, the proceedings on a patent application might not conclude and a patent might not issue until after FDA approved

the NDA. Congress provided a final opportunity for an applicant to obtain benefits of patent listing and exclusivity in subsection (c)(2) of section 355:

> ***If the patent information described in subsection (b) of this section could not be filed with the submission of an application under subsection (b) ... [because] a patent was issued after the application was approved under such subsection,*** the holder of an approved application shall file with the Secretary the patent number and the expiration date of any [such] patent....

21 U.S.C. §355(c)(2) (emphasis supplied).

However, there is nothing in either subsection (b)(1) or in subsection (c)(2) that even remotely suggests that Congress contemplated or intended to authorize what SmithKline has done: submit information on entirely new patents into perpetuity, regardless of NDA approval dates. Rather, the Act provides a bright-line rule that requires minimal agency resources and no analysis of patents to enforce: when an NDA holder files information on a patent issued after approval of the NDA, FDA need only consult the NDA to determine whether patent information already was filed with the application or before approval. If so, then no further patent information can be submitted.

SmithKline obtained approval of NDA 020-031 with the '723 hemihydrate patent information on December 29, 1992. Thus, as of December 29, 1992, the Act precluded SmithKline from listing additional patents in connection with NDA 020-031. FDA should never have received or considered additional patents for NDA 020-031 after December 29, 1992, especially when SmithKline did not even file applications for additional patents until years later.

21 U.S.C. §355(c)(2) permits the filing of patent information after approval of an NDA only where administrative delay caused ***no*** patent information to be filed with the NDA or during

the review process leading to approval in accordance with §355(b). SmithKline is not the victim of administrative delay in the PTO envisioned by §355(c)(2) regarding its '132 Form C and '423 Form A patents: SmithKline did not even ***file*** the relevant applications until ***more than two years*** after FDA approved NDA 020-031 and more than two years after SmithKline began marketing Paxil®. SmithKline simply cannot submit its '132 Form C and '423 Form A patents for listing.

To interpret the statute otherwise thwarts the legislative objective of encouraging generic competition and provides an NDA holder with opportunities to manipulate the patent system and FDA's procedures for listing patents. The purpose of the patent listing provisions is to place ANDA applicants and the public on notice of the scope of patent protection for the NDA-approved drug. *Abbott Laboratories v. Zenith Laboratories*, 934 F. Supp. 925, 934 (N.D. Ill. 1995)("the Orange Book provides notice to potential ANDA applicants of the patents which may protect the pioneer drug product, thus allowing them to provide the appropriate certification under [21 U.S.C. §355(j)(2)(A)(vii)] of the Act."). ANDA applicants thus are able to determine with some certainty, prior to investing into the production of a generic drug, the scope of the Hatch-Waxman obstacles to approval.

However, if an NDA holder is permitted, as SmithKline did here, to list for an indefinite and extended future period any new patents that issue, certainty evaporates into a wholly unpredictable minefield of

- exposure to multiple lawsuits;
- serial stays of FDA approval;
- loss of generic exclusivity periods; and
- virtually no guarantee of market entry;

even if the original "pioneer" patent has expired. This scenario would chill the incentive of generic manufacturers such as Apotex to make the substantial investments required to develop generic substitutes, prepare and prosecute ANDAs and undertake the major expense of defending Hatch-Waxman statutory patent infringement litigation.

That FDA should limit the filing of patent information subsequent to FDA's approval of the NDA only to situations where no patent information had been submitted prior to FDA approval is entirely consistent with FDA's previous statutory analyses rejecting the premise that patent owners should be able to list patents during an unlimited time frame.

When FDA considered what to do with patents submitted for listing beyond the 30-day period following issuance of a patent, FDA rejected a proposal that would have permitted the holder of an approved NDA to update its patent information at any time. FDA rejected this approach because:

> ***[I]t would allow for manipulation of the patent filing system by the holder of the NDA and could result in delays in approval of otherwise approvable ANDA's.*** For example, if patents could be filed at any time after issuance, the holder of the NDA could delay the filing of a patent, and subsequent publication, until within 30 months prior to the expiration of the latest-expiring patent. [The ANDA applicant] will then be required either to file a paragraph III certification and wait until the patent expires, or to file a paragraph IV certification and therefore initiate the procedure set out at section 505(c)(3)(C) and (j)(4)(B) [now renumbered as (j)(5)(B)]. This procedure requires that the agency wait at least 30 months, unless a short or longer period is judicially ordered, before it makes effective approval of the application. ***Even if the NDA holder is unsuccessful in defending the late-filed patent, it will have extended its period of market monopoly in a manner inconsistent with the intent of Congress when it struck the balance between protecting the patent rights of innovators and encouraging prompt and efficient entry of generics onto the market.***

Abbreviated New Drug Applications; Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338, 50,340 (Oct. 3, 1994) (emphasis supplied). The same concern for manipulation of the patent system and the provisions of Hatch-Waxman should inform FDA's interpretation of the statute with respect to the issues which this petition presents.

Here, SmithKline sued Apotex based on Apotex' Paragraph IV certification for the '723 hemihydrate patent. Apotex is thus subjected to a 30 month stay of approval, set to expire in December of 2000. SmithKline then sued Apotex, in a different forum, based on Apotex' Paragraph IV certification for the '423 Form A patent, starting a new 30 month stay of approval period, set to expire in February 2002. Even if SmithKline loses the second lawsuit, the stay of approval period could be extended from December 2000 up to February 2002. Should SmithKline list still more patents, such as the '842 tablet patent, as Apotex expects SmithKline will, Apotex will have to file still more Paragraph IV certifications and endure new lawsuits. SmithKline will move the end of the stay of approval even farther into the future. This result is precisely the worst-case scenario FDA identified: unjustified monopoly from an unending series of regulatory stays, postponed lawful generic entry to market, and discouragement of efficient entry of generics into the market. *Abbreviated New Drug Applications; Patent and Exclusivity Provisions*, 59 Fed. Reg. at 50,340.

Plainly, 21 U.S.C. §355(c)(2) does not permit SmithKline to "late-list" patents that issue subsequent to 1992, when FDA approved SmithKline's NDA 020-031 with its '723 hemihydrate patent. FDA should remove SmithKline's '132 Form C and '423 Form A patents from the Orange Book, because both the '132 Form C and '423 Form A patents were ***filed and issued***

after 1992, and are ineligible for "late-listing."

(b) If FDA Refuses To De-List Late Listed Patents, FDA Should Waive Certification Requirements.

SmithKline's patent warehousing prejudices rights which Congress granted Apotex under the Act. If FDA permits SmithKline to maintain listings for its 1999 patents, FDA at least should not require Apotex to file paragraph IV certifications. FDA similarly does not require additional paragraph IV certifications for pending ANDAs when subsequently submitted patents fail to comply with 21 U.S.C. §355(c)(2) – FDA simply lists the late-filed patents for public information without prejudicing pending ANDA rights. FDA has explained:

> The approach adopted by the agency ... best embod[ies] the compromise adopted by Congress [between protecting the patent rights of innovators and encouraging prompt and efficient entry of generics onto the market]. While this could result in two categories of ANDA's for a pioneer drug, those without certifications for the late-filed patent and those with certifications for that patent, this approach is the best means ***for discouraging manipulation of the patent filing scheme and providing optimum notice of applicable patents***.

Abbreviated New Drug Applications; Patent and Exclusivity Provisions, 59 Fed. Reg. at 50,340 (emphasis supplied). FDA similarly should preserve the rights of Apotex under the Act and should maintain the incentives which drove Apotex to file the first ANDA by determining that Apotex need not issue paragraph IV certifications for SmithKline's 1999 patents.

2. SmithKline Violated The Act When It Submitted Information On Patents That Do Not Claim The Drug For Which It Submitted NDA No. 020-031.

SmithKline also improperly caused FDA to list the '132 Form C and '423 Form A patents, because neither patent claims the drug which is the subject of NDA 020-031.

The Act limits the patent information that an NDA applicant or NDA holder may submit to:

> ...any patent which ***claims the drug for which the applicant submitted the application***...

21 U.S.C. §355(b) (emphasis supplied); 21 U.S.C. §355(c)(2) ("claims the drug for which the application was submitted"). Regardless of when the holder of an NDA submits patent information for an NDA, the patent must claim the NDA drug.

FDA's regulation on the subject is entirely consistent with the plain language of the statute. 21 C.F.R. §314.53(b) provides:

> (b) *Patents for which information must be submitted* .... For patents that claim a drug substance or drug product, the applicant shall submit information ***only*** on those patents that claim a drug product that is the subject of a pending or approved application, or that claim a drug substance that is a component of such product. For patents that claim a method of use, the applicant shall submit information ***only*** on those patents that claim indications or other conditions of use of a pending or approved application.

21 C.F.R. §314.53(b) (bold emphasis supplied). Moreover, FDA removed any ambiguity about its position, when FDA specifically rejected proposals to list "patents that claim drug products for which the patent owner is not seeking or has not obtained approval." *Abbreviated New Drug Applications; Patent and Exclusivity Provisions*, 59 Fed. Reg. at 50,346. FDA based its rejection upon the plain text of the Act. *Id.*

The Act's focus on patent ***claims*** simplifies the analysis. Although a patent often is a lengthy and complex document, its operative element–the claim or claims–is easy to identify. At the end of a patent, the claim or claims typically are prefaced with the phrase, "I claim." The claim or claims describe the invention. *See*, *Hoechst-Roussel Pharmaceuticals Inc. v. Lehman*, 109 F.3d 756, 758 (Fed. Cir. 1997); *Bell Communications Research, Inc. v. Vitalink Communications Corp.*, 55 F.3d 615, 619 (Fed. Cir. 1995) ("The language of the claim defines the scope of the protected invention"). As discussed below, only SmithKline's '723 hemihydrate patent, not its '132 Form C and '423 Form A patents, claim the drug that FDA approved in NDA 020-031.

(a) SmithKline's '723 Patent On Crystalline Paroxetine Hydrochloride Hemihydrate.

SmithKline filed its NDA for paroxetine hydrochloride hemihydrate – the drug that FDA approved. (Tab G, col. 1) ("It is the hydrochloride salt of a [paroxetine] hydrochloride hemihydrate and has the empirical formula of $C_{19}H_{20}FNO_3 \cdot HCl \cdot \frac{1}{2} H_2O$"). Claim 1 of the '723 hemihydrate patent, for which SmithKline filed patent information before FDA approval, consists of only four words:

1. Crystalline paroxetine hydrochloride hemihydrate.

(Tab A, col. 10). Plainly, claim 1 is for a hemihydrate paroxetine compound – *i.e.*, one that contains ½ molar equivalents of water ("$\cdot \frac{1}{2} H_2O$") for each mole of paroxetine hydrochloride. SmithKline acted properly in submitting patent information on the '723 hemihydrate patent in connection with NDA 020-031, and its publication in the Orange Book is consistent with the requirements of the Act.

(b) SmithKline's '132 Form C And '423 Form A Patents On Anhydrate Polymorphs Of Paroxetine Hydrochloride.

In 1999, SmithKline obtained issuance of the '132 Form C and '423 Form A patents patents on two anhydrate polymorphs of paroxetine hydrochloride. The '132 Form C patent contains the following claim:

> 1. Paroxetine hydrochloride **anhydrate in Form C**, which form comprises the following characteristics: [listings of data on melting point, infrared spectrum, thermal characteristics obtained by differential scanning calorimetry, X-ray powder diffraction peaks and ^{13}C-NMR peaks].

(Tab B, col. 17) (emphasis supplied). The '423 Form A patent similarly contains one claim:

> 1. Paroxetine hydrochloride **anhydrate in Form A**, which form comprises the following characteristics: [listings of laboratory data employing the same analytical methods described for the claim of the '132 Form C patent].

(Tab C, cols. 17-18) (emphasis supplied).

The two patents on their face do not claim the drug – paroxetine hydrochloride hemihydrate – which is the subject of NDA 020-031. There is no doubt that an "anhydrate" form is distinct from a hemihydrate form. Thus, it would not be possible for the '132 Form C and '423 Form A anhydrate patents to claim the FDA-approved paroxetine hydrochloride hemihydrate drug.[2]

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[2] If SmithKline asserted to the PTO that the '132 Form C and '423 Form A patents claim the drug that FDA approved in NDA 020-031 in 1992, the '132 Form C and '423 Form A patent claims would be invalid as a matter of law under 35 U.S.C. §102(b) because the drug was "on sale" more than one year prior to the date on which the patent applications leading to the '132 Form C and '423 Form A patents were filed in the United States. *See Abbott Laboratories v. Geneva Pharmaceuticals, Inc.*, 182 F.3d 1315, 1318 (Fed. Cir. 1999) (invalidating patent

The clear and unambiguous words of the statute, 21 U.S.C. §355(c)(2) ("applicant shall file...[information for] ***any patent which claims the drug for which the application was submitted***....), as well as FDA's regulation, are dispositive. SmithKline's submission of patent information on the '132 Form C and '423 Form A patents was unlawful because the patents fail to claim the hemihydrate product FDA approved in NDA 020-031.

(c) FDA Has The Competence And Resources To Police This Abuse Of The Patent Listing Provisions Of The Act.

Despite the bright lines that Congress enacted, FDA claims that it lacks the resources and competence to assure that only patents that claim the drug for which an NDA was submitted are published in the Orange Book. *See, e.g., Abbreviated New Drug Applications; Patent and Exclusivity Provisions*, 59 Fed. Reg. at 50,345. FDA assumes the responsibility only to inform the holder of an NDA of any complaint by another private party of an illegal or otherwise improper listing of a patent in the Orange Book. *See* 21 C.F.R. §314.53(f) regarding "correction of patent information errors." Apotex believes that FDA's position is not well-taken and that the regulation is invalid.

First, fewer than thirty patents were added to the patent lists in the Orange Book in 1999. (Tab H). Second, FDA has substantial resources and expertise for reviewing information on the chemical structure of a drug substance or of any other component of a drug product. With respect to drug substances, FDA requires applicants filing both NDA's and ANDA's to include

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because anhydrous polymorph was on sale more than one year prior to the filing date of the patent).

extensive and detailed information on chemical identification and characterization of the drug substance and supporting analytical studies. FDA routinely issues deficiency letters that reflect a high degree of sophistication in the analysis of such information. For instance, FDA was able to use its expertise to identify that Apotex's ANDA paroxetine product was an anhydrous material that was different from a hemihydrate, and directed Apotex to amend a clerical error in its proposed product insert accordingly. (Tab I). In addition, to the extent that FDA has any uncertainty in individual cases, it may ask the NDA holder for an explanation or may decide not to list the patent. *Pfizer, Inc. v. FDA*, 753 F. Supp. 171, 177 (D. Md. 1990).

Moreover, Congress required FDA to supervise patent filings. Congress granted FDA the power to sanction the failure to file patent information under 21 U.S.C. §355(c)(2) by withdrawing approval of an NDA. 21 U.S.C. §355(e). Congress explicitly tied this sanction – withdrawal of NDA approval – to affirmative FDA investigation into patent listings, because FDA may only invoke the sanction when such information "[is] not filed within 30 days after the receipt of written notice from the Secretary specifying the failure to file such information." The objective of this severe sanction is evident: prevent holders of approved NDA's from "warehousing" subsequently issued patents for later use against unsuspecting ANDA applicants.

An agency cannot ignore statutes that it must administer and enforce. The Supreme Court has recognized that an agency's decision not to enforce a regulation in an individual instance is a legitimate exercise of an agency's discretion that is effectively unreviewable; however, the Court noted that an exception to that rule occurs when "the agency has 'consciously and expressly adopted a general policy' that is so extreme as to amount to an abdication of its statutory

responsibilities." *Heckler v. Chaney*, 470 U.S. 821, 833 n.4 (1984) (allowing FDA to exercise its discretion to not enforce the Act's requirements for new drugs for drugs used for lethal injection); *see also Sierra Club v. Yeutter*, 911 F.2d 1405, 1412 (10th Cir. 1990) (finding no abdication of statutory responsibilities because the agency set forth affirmative actions the agency would take to protect wilderness water values).

The *Heckler* Court also noted that a reason why an agency's decision to not enforce a regulation in a specific instance is not reviewable is because the agency is not "exercis[ing] its *coercive* power over an individual's liberty or property rights," *Heckler*, 470 U.S. at 832 (emphasis in original). Here, FDA's refusal to monitor the contents of SmithKline's newly issued patents and to enforce the plaint text of the patent listing provisions of the Act has effectively coerced Apotex into filing unnecessary paragraph IV certifications, which immediately led to the improper second infringement lawsuit. Thus, FDA's administration of the patent lists is not an area where FDA is free to exercise its discretion to not enforce the statutory and regulatory requirements for listing.

Nor may FDA rely on private causes of action between ANDA applicants and NDA applicants to police the accuracy of patent listings in the Orange Book. Courts have "agree[d] with the general proposition that when Congress has specifically vested an agency with the authority to administer a statute, it may not shift that responsibility to a private actor...." *Perot v. Federal Election Com'n*, 97 F.3d 553, 559 (D.C. Cir. 1996); *see also Marathon Oil Co. v. Lujan*, 937 F.2d 498, 500 (10th Cir. 1991) ("Administrative agencies do not possess the discretion to avoid discharging the duties that Congress intended them to perform"). While the Court in *Perot*

determined that there was no delegation of authority to a private actor, its decision also noted that FEC substantively determined whether its regulations were, in fact, complied with. *Perot*, 97 F.3d at 560. FDA has made no such independent review here and therefore should not require Apotex to file an action for emergency injunctive relief essentially to have a court provide that review.

In short, FDA has the authority, expertise and obligation to ensure that listed patents actually claim the drug FDA approves in an NDA. It is plain that FDA will be able to look at SmithKline's '132 Form C and '423 Form A patent claims and, using its expertise, determine that the '132 Form C and '423 Form A patent claims for anhydrous material do not claim paroxetine hydrochloride hemihydrate. As such, FDA is capable of determining that SmithKline's '132 Form C and '423 Form A patents were listed in violation of the provisions of 21 U.S.C. §§ 355(b)(1) and (c)(2). Because SmithKline's abuse of the patent listing provisions to procure the publication of patents that do not claim the NDA drug is offensive to Congressional policy, FDA should assume an active role in policing the relevant provisions of the Act, and delist the '132 Form C and '423 Form A patents from the Orange Book.

3. FDA Should Not Permit SmithKline To Manipulate The Patent Listing System With Information On New Patents Without Submitting Either An ANDA, A New NDA, Or A Supplement To Its Approved NDA.

Independent of the issue of the timing and claim scope of SmithKline's new anhydrous polymorph patents, SmithKline violated both the Act and FDA's regulations by filing information on patents for two drug substances that FDA has not approved for marketing.

The Hatch-Waxman Amendments were designed to reward those who undertake the

arduous NDA approval process with unique procedural protections against FDA approval of generic versions of a patented drug, primarily through the patent listing procedure. Here, SmithKline has availed itself of the benefit of the patent listing provisions without undertaking the burdens, *i.e.*, doing the work and expending the resources to file an ANDA, a new NDA, or a supplemental NDA for an anhydrous form of a paroxetine hydrochloride product. Apotex, not SmithKline, has performed the necessary clinical trial work which will enable FDA to approve an anhydrous paroxetine hydrochloride product for marketing.

FDA approved SmithKline's NDA and listed the '723 hemihydrate patent covering paroxetine hydrochloride *hemihydrate*, not for anhydrous "Form A" or "Form C" paroxetine hydrochloride. SmithKline has filed no new NDA on either of the '132 Form C or '432 Form A anhydrous paroxetine polymorphs; SmithKline has filed no supplement to its NDA requesting a change in the approved drug from the hemihydrate form to either of the anhydrous forms; and SmithKline has invested in no new clinical studies to establish the safety, efficacy or bioequivalence of either of the anhydrous forms as FDA allows under 21 C.F.R. §314.53(d)(2).[3]

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[3] 21 C.F.R. §314.53(d)(2) reads as follows:

(2) *Supplements.* (i) An applicant shall submit patent information ... for a patent that claims the drug, drug product, or method of use for which approval is sought in any of the following supplements:

(A) To change the formulation;
(B) To add a new indication or other condition of use, including a change in route of administration;
(C) To change the strength;
(D) To make any other patented change regarding the drug, drug product, or any method of use.

If SmithKline wants to list its '132 Form C and '423 Form A patents because the allegedly new anhydrous polymorphs have important advantages compared to the hemihydrate, FDA should require that SmithKline demonstrate those advantages through new clinical studies. Absent a new or supplemental NDA, FDA should follow the approach it took in *Pfizer* and delist the '132 Form C and '423 Form A patents from the Orange Book. In *Pfizer*, FDA refused to list a patent on a tablet formulation of a drug product that was not covered by the approved NDA. The court agreed with FDA, and its decision correctly identifies the policy reasons for restricting the holder of an NDA to the listing of patents that claim the drug for which the NDA was submitted:

> Procardia was approved in 1981. The only additional protection at issue in this case is the notice of ANDA filing and the automatic 30-month stay for patent infringement litigation Pfizer could obtain if the FDA accepted for filing its patents on the unapproved tablet formulations. ***There is nothing in the legislative history to indicate that Congress intended to provide that protection as to a product Pfizer has chosen not to make available to the American public***. Procardia, the approved product, and nifedipine, its active ingredient, have received all the protection Congress determined to provide them under the 1984 amendments.

Pfizer, 753 F.Supp. at 177. Given that SmithKline's '132 Form C and '423 Form A patents cover "a product [SmithKline] has chosen not to make available to the American public," *id.*, as evidenced by its failure to file an NDA or NDA supplement for either of the anhydrous polymorphs claimed in those patents, FDA should de-list the '132 Form C and '423 Form A patents.

4. Countervailing Views.

Apotex acknowledges its obligation to present countervailing arguments known to it. 21 C.F.R. §10.30(b). Apotex is aware of an unpublished, non-final opinion of a U.S. District Court that would permit the holder of an approved NDA to list patents on drug substances other than that which the party submitted in an NDA application and which FDA has approved. *Zenith Laboratories, Inc. v. Abbott Laboratories*, No. 96-1661 (D.N.J. Aug. 5, 1996) (Tab J). The opinion is rife with errors, and the holding misconstrues the goals of the Hatch-Waxman Amendments.

In *Zenith*, the holder of an approved NDA on terazosin dihydrate filed, and FDA published, four patents on anhydrous polymorphs of terazosin. The plaintiff, which had filed an ANDA on an anhydrous form of the drug, sued the NDA holder for damages and an injunction requiring the NDA holder to delist these patents. The court, in apparent ignorance of FDA's regulation refusing to police the listing of patents, stated that FDA had "approved" the anhydrous polymorph patents for listing. *Zenith*, Slip Op., at 20, 21. The court, in an additional display of confusion, also stated that FDA had "approved" drug substances consisting of the anhydrous polymorphs, even though it stated earlier in its opinion that the drug being marketed by Abbott (and, presumably, the drug that FDA had approved) was the dihydrate form. *Id.*, at 6, 21.[4]

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[4] The extent of the court's confusion and its utter failure to grasp the essential elements of the statutory scheme is illustrated by the following: "Zenith argues that, although the FDA found that the [anhydrous] patents are covered by Hytrin, which must be undisputed as the FDA approved and listed each of the contested patents, this does not necessarily mean that the patents are actually covered by, or claim, Hytrin." Slip Op., at 21-22. As the court said earlier, FDA had approved Abbott's NDA on the ***dihydrate*** form, which Abbott then marketed under their

The *Zenith* court simply failed to distinguish between the quite different statutory requirement for the listing of patents in 21 U.S.C. §§ 355(b)(1) and (c)(2) from the "same active ingredient" element of 21 U.S.C. §355(j)(ii)(A)(ii)(I) governing ANDA contents:

> [I]f the listed drug ... has only one active ingredient, [the ANDA applicant must include] information to show that the active ingredient of the new drug is the same as that of the listed drug...

As FDA's responses to other citizen petitions (which the *Zenith* court had before it, but did not understand) have stated, a proposed generic version of a listed drug may have a different polymorphic form yet still be the "same" as the approved pioneer drug, *provided that the ANDA applicant establishes that they are bioequivalent. See* Response of FDA to Citizen Petition of Janssen Research Foundation, dated July 1, 1994, Docket No. 88P-0369/CP & PSA, at 4 (Tab K); *see also*, Response of FDA to Citizen Petition of Bristol-Myers Squibb Co., dated Apr. 6, 1992, Docket No. 90P-0240/CP, at 3 (recognizing that hydrated and anhydrous forms may be the "same" for FDA purposes if bioequivalence is established) (Tab L).[5]

In sum, the final, published decision in the *Pfizer* case established the correct result, not the unpublished, interlocutory opinion in *Zenith*. Following *Pfizer*, FDA should remove SmithKline's '132 Form C and '423 Form A anhydrous polymorph patents from the Orange Book

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trademark Hytrin. *Id.* at 6. Moreover, the court failed entirely to deal with FDA's current regulatory position, under which it never "approves" or "disapproves" the listing of patents in the Orange Book.

[5] FDA takes the same position in the advisory therapeutic equivalence evaluations in the Orange Book: "Anhydrous and hydrated entities are considered pharmaceutical equivalents and must meet the same standards and, where necessary, ... their equivalence is supported by appropriate bioavailability/bioequivalence studies." Approved Drug Products with Therapeutic Equivalence Evaluations, xii (16th ed. 1996).

Conclusion.

There are three separate, independent grounds for removing the '132 Form C and '423 Form A patents patents from the Orange Book. First, SmithKline improperly induced FDA to list the '132 Form C and '423 Form A patents even though those patents were ***filed and issued*** too late for listing. Second, neither the '132 Form C or '423 Form A patents claim the paroxetine hydrochloride hemihydrate drug FDA approved in NDA 020-031. Third, SmithKline listed the '132 Form C and '423 Form A patents without submitting a new or supplemental NDA with clinical trial data for the anhydrous paroxetine compounds claimed by those patents.

This petition presents the straightforward statutory – not technological – bases to enable FDA to follow its own precedents to undo SmithKline's inappropriate effort to abuse the patent listings that FDA adminsters. FDA should remove the '132 Form C and '423 Form A patents from the Orange Book, refuse to list any further patents SmithKline submits for NDA 020-031 and refuse to consider the '132 Form C and '423 Form A patents in connection with FDA's analysis of the approvability of Apotex ANDA 075-356.

FDA should act immediately to remove the '132 Form C and '423 Form A patents from the Orange Book to forestall further efforts by SmithKline to prolong its monopoly on paroxetine hydrochloride drugs through abuse of the patent listing provisions of the Hatch-Waxman Act. Moreover, the prospect of serial issuance of further patents (such as the '842 tablet patent, Tab M), further lawsuits and further stays of generic drug approval during the rest of this decade and beyond, along with the consequent illegal extension of SmithKline's monopoly through abuse of the FDA listing procedures is intolerable and should prompt FDA to act now.

C. Environmental Impact

The actions requested by this petition are subject to categorical exclusion pursuant to 21 C.F.R. §25.30.

D. Economic Impact

An Economic Impact Statement will be made at the request of the Commissioner.

E. Certification

The undersigned certify, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

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